REMARKS

The Amendments to the Specification beginning on page 16, line 35, on page 18, line 8, on page 25, line 24, on page 35, line 7, on page 40, line 5, on page 41, line 11, and the first amendment to the paragraph beginning on page 43, line 12 were made to correct typographical errors.

The Amendment to the Specification in the paragraph beginning on page 43, line 12 (in Example 5) amending the sentence "The treatment group received 1000 mg/Kg~~/day~~ of lanthanum carbonate administered orally twice daily" was made to correct an obvious typographical error. The statement that "1000 mg/Kg/*day* of lanthanum carbonate administered orally twice *daily*," (emphasis added) is nonsensical. This statement is amended by way of this amendment to reflect what was done in these animal studies, i.e. oral administration of 1000 mg/Kg of lanthanum carbonate twice daily. As demonstrated in the attached page (annexed as Exhibit 1), which is a page of the study used as a basis for Example 5, the highest lanthanum dosage given to dogs was 1000 mg/kg, twice daily (i.e. half of the total daily dose of 2000 mg/kg (1000 mg/kg) was administered twice daily). A typographical error was made while transferring information from the study to Example 5. No new matter has been added by way of this amendment and Applicants respectfully request its entry.

The Amendment to the Specification in the paragraph beginning on page 43, line 12 (in Example 5) deleting the measured parameter "Incorporation of lanthanum within bone (modified solochrome azurine technique)," which is the only reference in the specification to whether lanthanum is incorporated into the bone, was made to correct an inadvertent error. When the experiment used as a basis for Example 5 was performed, those skilled in the art believed that the modified solochrome azurine technique had the sensitivity to detect lanthanum in bone (see page 2 of annexed Exhibit 2, which is a copy of a report that was used as a basis for Example 5). Thus, this technique was used to determine lanthanum incorporation and based on the results, it was concluded that no lanthanum was present in the bone (see page 44, lines 13-15, which is the only reference to this interpretation of the results in the specification). However, subsequent to the study, it was

determined that this technique did not have the sensitivity required to detect lanthanum incorporation into the bone of animals orally dosed with lanthanum. The Applicants respectfully request deletion of the phrase "Incorporation of lanthanum within bone (modified solochrome azurine technique)" from the specification as this test did not have adequate sensitivity and its inclusion in the specification was an inadvertent error that occurred without deceptive intent.

CONCLUSION

No new subject matter has been added as a result of the amendments; no new search is required, and no new issues are raised. Inasmuch as the above amendments enter corrections of formal matters and do not affect the substance of the application, it is respectfully requested that the Patent and Trademark Office enters the amendments set forth above.

The Examiner is invited to contact the undersigned directly with any questions or concerns at 212.527.7687.

Dated: April 27, 2005

Respectfully submitted,

By _____

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1.0 SUMMARY

1.1

Sixteen male and sixteen female beagle dogs were divided into four groups, each comprising four males and four females. Three groups received lanthanum carbonate, in capsules at dose levels of 200, 600 or 2000 mg/kg/day. The fourth group received empty gelatin capsules and acted as a control. Individual doses were adjusted according to the most recently recorded bodyweight. Animals were dosed twice daily, approximately three hours apart for at least 13 weeks and received half of the daily dose on each occasion.

Clinical observations and food consumption measurements were performed daily throughout the study. Bodyweights were recorded weekly. Ophthalmoscopy and clinical pathology assessments were performed for all animals before the start of treatment and during week 13. Additional urine samples were obtained during week 6 and 12 for assessment or urine calcium and phosphate levels. Blood samples were obtained from all animals at the end of the treatment period for assessment of plasma levels of the test article and for the assessment of parathyroid hormone levels.

At the end of the treatment period all the animals were necropsied and subjected to organ weight measurements and macroscopic examination. A detailed histopathological examination was performed for all animals.

1.2

All animals survived the treatment period.

1.3

Treatment-related clinical signs included isolated incidences of dark, oily, liquid faeces for some animals given 2000mg/kg/day.

1.4

Bodyweights and food consumption were unaffected by administration of lanthanum carbonate.

1.5

Haematological investigations did not reveal any treatment-related effects.

1.6

Blood chemistry evaluation showed a decrease in inorganic phosphate levels for males given 2000 mg/kg/day, values were however within the quoted reference range. During week 13 the group mean alkaline phosphatase (ALP) and alanine aminotransferase (ALT) values for those females dosed at 2000 mg/kg/day were elevated. This was due to the high values obtained for animal 4F, 80.

[redacted]

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Dear Dr Moyce

I have now completed the analysis of tissue sections from 16 of the 32 dogs as requested. The specimens that have been analysed are taken from the iliac crest of dogs nos 51 - 58 and 75 - 82 inclusive. The odd numbered animals are males, the even numbered animals are females, the first group are control animals and the second had the high dose of the treatment.

Samples of bone were taken vertically through the iliac crest, embedded in methyl-methacrylate based resin, sectioned and stained with Toluidine Blue and Von Kossa stain. The sections were examined subjectively and also by interactive histomorphometry. The parameters measured were, trabecular and cortical bone mass, osteoid surface and volume, osteoblast surface, cortical osteoid volume, trabecular and cortical osteoclast number, resorptive surfaces in cortex and trabecular bone and, in addition, we have used a modified solochrome azurine technique for identifying the presence of lanthanum within bone.

Results

The iliac crest in these animals is acting as a growth plate. The appearances are those of immature animals that are actively growing. There is very active bone remodelling throughout the specimens sampled and, in addition, there appears to be bone modelling with very active periosteal osteoclasis on one cortical surface, and within the cortex on the other.

The other noticeable feature was a marked difference in cortical thickness between the different animals and marked variation in the amount of bone within the biopsy specimen. This degree of variation was not restricted to either of the two groups of animals, or to animals of a particular sex. There was no statistically significant difference in any of the bone parameters investigated between the two groups, with the exception of the trabecular bone volume which was lower in the control group than in the high dose lanthanum treated group.

Our stain for lanthanum took some time to develop and we have not had an opportunity to test it in animal tissues, all the work having been done in paper chemical systems. The stain is not specific for lanthanum, it will also detect iron and aluminium but the reaction products are of different colour. We have failed to identify lanthanum within the bone of these dogs, but have noticed, in many animals, including controls, a staining line deep within bone. The nature of this is unclear, but we wonder whether the animals might have received iron or aluminium supplements some while before death.

Interpretation of the investigations

On a the specific question of lanthanum being taken up into bone, we have failed to show any evidence for this. The sensitivity of the technique looks as if it is very similar to that we have used in identifying aluminium within bone, giving detection limits of round about 30 parts per million dry weight. In the absence of any lanthanum loaded bone to test however, this figure cannot be taken with certainty but all the evidence points towards this being a ballpark figure. Taking high doses of the lanthanum salt does not in any way seem to have affected current bone cell parameters. What was surprising was the presence of an increased trabecular bone volume in the treated animals. Although there was considerable variation in the trabecular bone volume between animals, in the treated animals it was approximately twice that in the controls. In the absence of any measurable change in osteoblastic or osteoclastic activity the explanation for this is most likely one of the following:-

1 That the changes in the bone cell activity although significant in biological terms, cannot be measured using conventional histomorphometric techniques.

2 That we are dealing with an artefact related to the broad diversity of the animals' bone structure and that the apparent differences are effectively a sampling error.

3 That in some way the lanthanide influences bone growth at the growth plate, (on which we do not perform histomorphometry), these animals still being in a growing phase.

What I would suggest is that if you are agreeable we can investigate this by measuring the bone mass in the biopsies in groups 2 and 3. The time consuming element in this analysis is performing full histomorphometric data, but the measurement of bone mass is undertaken automatically and we would be willing to analyse these further 16 specimens at no extra charge to your organisation. We would of course let you know as soon as the information were available because of the implications for the use of this product in the management of low bone syndromes including osteoporosis.

There is some scientific basis for this in that it is known aluminium and strontium are both capable of stimulating osteoblastic activity.

In summary, we have failed to identify lanthanum within the tissues using our histochemical techniques. There are some differences in bone volume between the 2 groups of animals, but their significance needs to be investigated further. There is no difference that we can detect using histomorphometry in bone cell activity in these animals, although it must be recognised that they would still appear to be growing and that their bone is undergoing very high turnover.

We should like your permission to go ahead and examine the bone mass in specimens 59 to 74 at no extra cost to your organisation.

Please find enclosed our invoice for services already conducted for £1,920.

Yours sincerely

A J Freemont
Professor of Osteoarticular Pathology